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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/941,314	08/29/2001	James L. Holloway	00-81	6794

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EXAMINER	
YU, MISOOK	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/941,314	HOLLOWAY ET AL.	
	Examiner	Art Unit	
	MISOOK YU, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 May 2003 and 07 July 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-9* is/are pending in the application.

4a) Of the above claim(s) *1, 3 and 4* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of group 2, drawn to a polypeptide in Paper No. 7 is acknowledged. Applicant's election of species i.e. SEQ ID NO: 7 in Paper No. 11 is also acknowledged. The preliminary amendment (Paper No. 7) cancels claim 2, drawn to the polypeptide (i.e. the elected invention), but adds new claims 5-9, drawn to the polypeptide.

Claims 1, 3, 4, 5, 6, 7, 8, and 9 are pending. Claims 1, 3, and 4 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 7.

Claims 5, 6, 7, 8, and 9 are examined on merits.

Specification

The disclosure is objected to because of the following informalities: the first line of the specification says that the instant application claims the benefit of the US Provisional Application No. 60/230,230 filed September 1, 2001. However, the provisional application was filed in 2000.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5-9 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 5-9 are interpreted as drawn to a genus of isolated polypeptides comprising a fragment of SEQ ID NO: 2, wherein said fragment comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 3-17. The specification at page 60, lines 21-28 teaches that SEQ ID NOs: 3-17 are fragments of a newly isolated 137 amino acids human polypeptide i.e. SEQ ID NO: 2.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claims is a partial structure i.e. SEQ ID NOs: 3-17. Claims 5-9 do not recite a functional characteristic coupled with the partial structure. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the

'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, given that the specification has only described one full-length polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 3-17. Therefore, an isolated polypeptide comprising SEQ ID NO:2 only, but not the full breadth of the claims meets the written description provision of 35 U.S.C. §112, first paragraph.

Claim 8 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 8 is drawn to an isolated polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 2-17, wherein said polypeptide further comprises "a detectable label". Applicant is kindly requested to point out the support in the specification as originally filed for attaching "a detectable label" to an isolated polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 2-17 since the support is not apparent to the Office.

Claim Rejections - 35 USC § 101

Claims 5, 6, 7, 8, and 9 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility, or a well established utility.

The specification asserts that the disclosed invention can be used for: making a variant and an antibody (page 58), and a fusion protein by linking the instantly claimed invention to polyHistiding tags (page 40), to other therapeutic agents such as insulin (page 41, line 14), and to antibody fragment (page 42); diagnostic applications (page 65-70); promoting spermatogenesis (page 73, line 29), enhancing fertilization during assisted reproduction (page 86, line 31), enhancing sperm production, and increasing the number of viable sperm (page 87, line 8); inhibiting cancer procoagulant protein (page 87, line 25 to page 88, line 3); or educational kit (page 88). These utilities are not considered to be specific and substantial or well established because neither the specification nor any art of record teaches what the biological function(s) or biochemical activity of the newly discovered SEQ ID NO:2 polypeptide is.

The specification teaches SEQ ID NO:2 is a newly isolated 137 amino acids human polypeptide named Zcy8. The specification at page 60, lines 21-28 teaches that SEQ ID NO: 3-17 are fragments of SEQ ID NO: 2. The specification at page 89, lines 24-26 discloses Zcy8 was discovered in placenta cDNA library and Zcys8 is expressed in colon and testis. The specification states at page 2, lines 18-20 that SEQ ID NO:2 is "a novel cystatin...referred as Zcys8"; this is interpreted as saying the instantly claimed SEQ ID NO:2 belongs to cystatin superfamily of protein based on homology to other known cystatin family proteins. The specification at pages 1-2, and 5 reviews that:

cystatin superfamily consists of at least three subfamilies i.e. family 1, 2, and 3; and some of the proteins belong to the superfamily have known biological and biochemical activities; and cystatin-related proteins (CRES) are also known.

It appears that the asserted utility for instantly claimed invention is based on structural homology to other known multiple proteins that belong to cystatin superfamily or CRES. The specification does not teach which protease(s) or which cancer procoagulant(s) the instantly claimed polypeptide inhibits if it is indeed a protease inhibitor. Cornwall et al (2003, Endocrinology, vol. 144, pages 901-8) teach at Fig. 1 that cystatin C and the specific CRES prepared from the 366-bp CRES cDNA (note page 902, under the heading "Preparation of histidine (His) fusion proteins") inhibit different proteases, although both belong to "cystatin" superfamily of proteins. This art was published almost three years after the effective filing date of the instant application and the authors of the art are still trying to figure out which cystatin inhibits which protease(s) in *in vitro* studies. Further, Cornwall et al (2003, Molecular and Cellular Endocrinology, vol. 200, pages 1-8) teach most of the newly discovered CRES , a new subgroup of the family 2 cystatins expressed in testis require more studies "to identify their functions" (note page 7, left column, the last paragraph). In summary, Cornwall et al (2003, Endocrinology, vol. 144, pages 901-8) and Cornwall et al (2003, Molecular and Cellular Endocrinology, vol. 200, pages 1-8) teach that there are numerous cystatins and CRES, each of the cystatins appears to be working on a specific protease, and has a different biological function, although these cystatins belong to the same superfamily having a common structural domain and sequence homology.

Based on what is known about "cystatin" in the art at the time the instant application was filed and teachings of instant specification, one in the art would conclude that instant invention might have "potential role as an object of use-testing" (Brenner v. Manson, 148 USPQ at 696) in modulating seminal fluid viscosity by inhibiting enzymatic activity, enhancing viability of cryo-preserved sperm, enhancing sperm mobility and fertilization in assisted reproduction, or inhibiting a cancer procoagulant protein. Since EQ ID NO: 2 does not have specific and substantial utility, or a well established utility, a compound that binds to SEQ ID NO: 2 does not have specific and substantial utility, or a well established utility.

The art generally acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. Scott et al (Nature Genetics, 1999, 21:440-443) teach that the function of newly identified gene products is unpredictable even when the database searches reveal significant homology to proteins of known function. Scott et al teaches that the gene causing Pendred syndrome encodes a putative transmembrane protein designated pendrin. Based on sequence similarity data, the authors postulated that the putative protein was deemed to be a member of sulfate transport proteins that included a 29% identity to rat sulfate-anion transporter, 32% similarity to human diastrophic dysplasia sulfate transporter, and 45% similarity to the human sulfate transporter 'downregulated in adenoma'. However, upon analyzing the expression and kinetics of the protein, the data revealed no evidence of sulfate transport wherein results revealed that pendrin functioned as a transporter of chloride and iodide. Scott et al. state that these results underscore the importance of

confirming the function of newly identified gene products even when the database searches reveal significant homology to proteins of known function (page 411, 1st column, 4th paragraph). Skolnick et al. (2000, Trends in Biotech. 18:34-39) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, p. 36). Similarly, Bork (2000, Genome Research 10:398-400) states that the error rate of functional annotations in the sequence database is considerable, making it even more difficult to infer correct function from a structural comparison of a new sequence with a sequence database (see especially p. 399). Such concerns are also echoed by Doerks et al. (1998, Trends in Genetics 14:248-250) who state that (1) functional information is only partially annotated in the database, ignoring multi-functionality, resulting in under-predictions of functionality of a new protein and (2) over-predictions of functionality occur because structural similarity often does not necessarily coincide with functional similarity. Smith et al. (1997, Nature Biotechnology 15:1222-1223) remark that there are numerous cases in which proteins having very different functions share structural similarity due to evolution from a common ancestral gene. Brenner (1999, Trends in Genetics 15:132-133) argues that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, then most homologs must have different molecular and cellular functions. Bork et al. (1996, Trends in Genetics 12:425-427) add that the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a small domain of the new protein

to a small domain of a known protein. Such questionable interpretations are written into the sequence database and are then considered facts. Finally, Bowie et al. (1990, Science 247:1306-1310) state that determination of three dimensional structure from primary amino acid sequence, and the subsequent inference of detailed aspects of function from structure is extremely complex and unlikely to be solved in the near future (p. 1306). Thus, the specification fails to support the asserted specific and substantial utility of the newly identified instantly claimed protein.

Furthermore, the specification does not teach a relationship to any specific disease or establish any involvement of SEQ ID NO: 2 polypeptide or any polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 3-17 in the etiology of any specific disease. The specification does not have any specific use for the educational kit comprising the polypeptide. Any polypeptide could be used in an educational kit, and for making antibodies, or fusion proteins.

Since the specification at page 2, lines 18-26 teaches that the invention is a novel isolated polypeptide (named as "Zcys8") comprising SEQ ID NO: 2, claims 5, 6, 7, 8, and 9 are interpreted as drawn to an isolated polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 2-17. The invention for the purpose of determining patentability under 35 U.S.C. 101 is limited to the claimed invention i.e. an isolated polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 2-17. The dependent claims 6-9 have limitations "an antibody fragment", "a therapeutic agent", "a detectable label", and "an affinity tag". Attaching instantly claimed polypeptide lacking utility to an art-known product that is not

the invention disclosed in the instant application, does not lead one skilled in the art to a readily available and practical use of the instantly claimed invention because one would still not know where said polypeptide targets the art-known attached product(s) and what its' effects would be.

Further research is required to use the instantly claimed invention for: diagnostic applications (page 65-70); promoting spermatogenesis (page 73, line 29), enhancing fertilization during assisted reproduction (page 86 line 31), enhancing sperm production, and increasing the number of viable sperm (page 87, line 8); inhibiting cancer procoagulant protein (page 87, line 25 to page 88, line 3).

After further research, a specific and substantial utility might be found for the claimed invention. The instant application has failed to provide guidance as to how one of skill in the art could use the claimed invention in a way that constitutes a specific and substantial utility. The proposed uses of the claimed invention are simply starting points for further research and investigation into potential practical uses of the claimed polypeptide. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner v. Manson*, 148 USPQ at 696.

Claims 5-9 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MISOOK YU, Ph.D. whose telephone number is 571-272-0839. The examiner can normally be reached on 8 A.M. to 5:30 P.M., every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne C Eyler can be reached on 571-272-0871. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

MISOOK YU, Ph.D.
Examiner
Art Unit 1642